DETERMINING STIMULATION LEVELS FOR TRANSCRANIAL MAGNETIC STIMULATION

FIELD OF THE INVENTION

[0001] The present invention relates to the field of electrical brain stimulation for the treatment of various illnesses. In particular, the invention relates to a method and apparatus for determining stimulation signal levels for applying electrical brain stimulation to a patient.

BACKGROUND OF THE INVENTION

[0002] Current methods of determining motor threshold (MT) position and stimulation levels for transcranial magnetic stimulation (TMS) studies rely on visual observation and interpretation of induced twitching of the thumb (i.e. abductor pollicis brevis) or by electromyography (EMG), which involves observation and interpretation of electrical response waveforms. In particular, a common method is to stimulate the motor cortex, observe thumb twitch or observe when the desired EMG signal exceeds a threshold value (i.e. motor evoked potential, MEP) as the stimulation level is manually adjusted. Both techniques are time consuming and highly dependent upon the skills and training of the practitioner. A more automated technique is desired that is not so operator dependent and time consuming. Such a technique should ideally provide simple feedback to the operator or may be used to close the loop to automate the motor threshold position determination process.

[0003] It would be advantageous to more directly determine desired levels for stimulating non-motor areas of the brain (e.g. prefrontal cortex); however, such techniques have not yet been developed. Direct measurement of evoked potential for non-motor areas using EMG techniques has been proposed by Sarah Lisanby, M.D. Unfortunately, direct measurement

of evoked potential is not straight-forward since neurons that are directly stimulated are not readily accessible with non-invasive techniques. Functional magnetic resonance imaging (fMRI) or positron emission tomography may be used to observe levels of neuronal stimulation, but these methods are expensive, would require TMS procedures to be performed at a facility with this equipment, and are logistically impractical for routine clinical TMS therapy. Indirect methods such as observation and interpretation of electroencephalogram (EEG) signals may be possible and are generally described herein.

[0004] Numerous search algorithms to determine the optimal stimulation level have also been proposed and tested clinically. For example, a procedure often used in TMS research estimates the motor threshold at a stimulus strength where 5 successes are observed within 10 stimuli. Another approach estimates the arithmetic mean of an upper threshold (smallest stimulus strength with 10 successes in 10 trials) and a lower threshold (largest stimulus strength with no success in 10 trials). Professor Friedemann Awiszus (Magdeburg, Germany) describes another search strategy for threshold estimation called the PEST (parameter estimation by sequential testing) algorithm in a publication titled "TMS and Threshold Hunting." The PEST algorithm uses adaptive threshold hunting to estimate the threshold continuously throughout the stimulus sequence where the stimulus strength that is to be used for the next stimulus is calculated from the information obtained from the previous stimuli.

[0005] The block diagram of Figure 1 shows the typical motor threshold level determination procedure used today. In this case the operator 10 operates a TMS stimulator 20 that provides pulses to a stimulation magnet 30 for application of TMS signals to a patient 40. The operator 10 receives direct visual feedback from the patient 40 or from an EMG display (not shown). The stimulation level and/or position is then adjusted manually by the operator 10 and the process repeated until a level is attained where half of the stimulation pulses result in a valid detected movement of the thumb. This approach can be augmented by employing an offline search algorithm 50, such as the PEST algorithm, to aid in selecting stimulation values based on prior responses. Use of the PEST algorithm is reflected by the diagram in prior art Figure 2.

[0006] It is known to monitor patient movement to detect evidence of seizure activity. For example, Gliner discloses in U.S. Patent Publication No. US 2003/0074032 A1 a neural stimulation system that uses a sensing unit to detect evidence of seizure or other collateral neural activity in response to an applied neural stimulation. The sensing unit may be an EEG monitoring device, a cerebral blood flow (CBF) monitor, a neural tissue oxygenation analysis device, or an electromyography device. In one embodiment, the monitoring device may also comprise a set of motion detectors, strain gauges, and/or accelerometers configured to detect or

monitor one or more types of patient movements that may be indicative of seizure activity. However, Gliner does not suggest how such a system may be used to detect motor threshold positions and levels and does not suggest correlating induced movement in the patient with a stimulation pulse to find the motor threshold position. On the contrary, the Gliner system stops the application of neural stimulation when a potential seizure or other collateral neural activity is detected. Moreover, Gliner is focused on seizure detection/prevention which is a very different purpose and involves detecting very different signal characteristics than proposed in accordance with the present invention. In the present application, the inventor is interested in detecting and observing "normal" levels of nerve stimulation, even though the stimulation is induced with a magnetic field. Seizures are a different phenomenon that typically occur at very much higher levels of magnetic stimulation (e.g. >2 times the MT level).

[0007] None of the prior art techniques known to the inventor suggests how to directly detect induced physical movement and how to correlate detected induced movement with TMS stimulation levels in order to determine TMS treatment stimulation levels or motor threshold. Prior art techniques do not describe methods of separately determining cortical depth and levels of neuronal excitability for the purpose of setting TMS stimulation levels. The prior art also does not teach techniques of determining TMS stimulation levels by observation and analysis of indirect signals such as EEG and its derivatives. The present invention addresses these needs in the art.

SUMMARY OF THE INVENTION

[0008] The present invention addresses the above-mentioned needs in the art by providing a means to detect induced movement or other activity in the patient and to correlate such movement or activity with a TMS stimulating pulse so as to determine the proper stimulation level at which to treat the patient, i.e., typically the motor threshold (MT) level. For example, the present invention may use an adaptive filter or correlator that is trainable by operator confirmation of a valid stimulation and means of providing direct visual or audible feedback to the operator that a valid stimulation has occurred.

[0009] In a first embodiment of the invention, motion detectors are used to detect specific patient movements and the motion detection outputs are provided via a feedback path to the TMS stimulator. The feedback path includes a valid motion stimulation detector that correlates the detected movement to the TMS stimulating pulse using, for example, a correlator or an adaptive filter. It is important to differentiate patient-initiated movement from stimulation-induced movement; therefore, correlation with the stimulation signal and isolation of specific muscle group movement is needed to specify when a true TMS stimulation has occurred. In the simplest implementation, the operator of the TMS stimulation equipment observes the output of

the valid motion detector and enters whether a successful stimulation has occurred (or not) to an algorithm such as PEST which assists in computing the next stimulation level to try. A series of stimulation values are tried until they converge to the MT value which is then used to set the treatment stimulation level. In another variation of the invention, the valid motion detection signal may be directly provided to the algorithm without user intervention.

[0010] In a second embodiment of the invention, the motion detectors are replaced with direct motor evoked potential (MEP) measurement devices that measure induced neurological voltage and correlate the measured neurological change to the TMS stimulus. An EMG system is used to detect a waveform that is correlated with a valid stimulus. As in the first embodiment, a feedback loop (with or without an operator) is used to seek convergence to the motor threshold value.

[0011] In a third embodiment of the invention, a signal is detected other than one caused by physical motion and that also has a strong correlation to specific focal stimulation of target areas of the motor cortex. For example, left/right asymmetry changes in a narrow subset of EEG signals derived from electrodes placed on the forehead of the patient (or elsewhere), or fast autonomic responses, such as skin conductivity, modulation of respiration, reflex responses, and the like, may be detected. In another variation of the invention, the indirect signals may be correlated to stimulation of non-motor areas of the brain such as the prefrontal cortex.

[0012] In a fourth embodiment of the invention, the appropriate stimulation level for TMS studies is determined using techniques other than motor cortex motor threshold methods. There are two parameters that affect proper setting of TMS stimulation levels: cortical depth and level of neuronal excitability. Desired stimulation is proportional to the product of these parameters. This embodiment separately determines each of these two parameters. A localized ultrasound probe may be used to determine the depth of cortical tissue at the treatment site. Alternatively, a localized and specifically designed probe may be used to detect impedance changes or filling factor differences when the probe is placed on the scalp at the desired treatment site. Such a probe may be constructed using a tuned coil and detection circuit that is sensitive to loading differences encountered when different biological tissue is placed in its proximity. The probe may be calibrated by observing impedance or Q factor (i.e. frequency*inductance/resistance) at a location where cortical depth is known from other methods such as ultrasound or standard motor threshold methods. Linearity and sensitivity must be determined by conducting these observations over a range of tissue depths, locations and subjects. An alternative variation of this probe is to transmit a radiofrequency (RF) pulse through this tuned circuit to the patient's head at the proposed stimulation site and observe the

absorbed power compared to that at a known cortical depth. These methods rely on loading differences between cerebral spinal fluid and cortical tissue and therefore require a high degree of sensitivity and appropriate calibration. Once the cortical depth is determined the neuronal excitability may be estimated by a number of standard neurological and/or psychological measures, including but not limited to EEG signal analysis (or subset thereof), measurement of autonomic response times, and depth of awareness measures (e.g. Aspect Medical, Inc. bispectral index or BIS^{TM}).

BRIEF DESCRIPTION OF THE DRAWINGS

[0013] The above-mentioned features and advantages of the invention will be apparent from the following detailed description in conjunction with the drawings, of which:

[0014] Figure 1 illustrates a conventional motor threshold level determination procedure.

[0015] Figure 2 illustrates the use of the PEST algorithm with the procedure of Figure 1.

[0016] Figure 3 illustrates an embodiment of the invention using a motion detector to detect patient movement for correlation to the TMS stimulation pulse.

[0017] Figure 4 illustrates a further embodiment in which the operator is removed from the feedback loop of the Figure 3 embodiment.

DETAILED DESCRIPTION OF ILLUSTRATIVE EMBODIMENTS

[0018] A detailed description of exemplary embodiments of the present invention will now be described with reference to Figures 3 and 4. Although this description provides detailed examples of possible implementations of the present invention, it should be noted that these details are intended to be exemplary and in no way delimit the scope of the invention.

[0019] Prior to TMS, the patient's motor threshold (MT) position is determined and the stimulation position is determined in reference to the MT position. The magnetic flux density, B, produced by the TMS therapy coil is adjusted with the coil positioned at the MT position in order to determine the MT stimulation level. This level is variable from patient to patient or over time for a given patient. Therefore, this procedure may have to be repeated. A simple and repeatable process to facilitate setting the MT stimulation level is thus advantageous in the clinical TMS procedure. The TMS therapy stimulation level is set as a relative percent of this MT value, so an accurate determination of MT level is important for systematic and safe TMS therapy.

Motion Detection Methods

[0020] The motor threshold position for TMS therapy is the coil position over the motor cortex at which the applied stimulus causes physical movement or twitching of the abductor

pollicis brevis muscle (i.e. thumb) on the contralateral hand. Conventional detection methods use the operator's observations and/or measurement of electrical response waveforms (i.e. EMG). A first embodiment of the present invention shown in Figure 3 improves upon such techniques by providing a motion detector including sensors 60 to detect patient movement (as opposed to relying upon operator observations. Sensors 60 provide motion detection outputs in a feedback path to the TMS stimulator 20 via signal processor 70, valid motion stimulation detector 80 and search algorithm 50 as shown in Figure 3.

[0021] Several technologies that may be used for the motion detector 60 include:

1) Physical motion sensors (e.g. LVDT, strain gauge, linear potentiometer, digital encoder);

2) Optical motion sensors (e.g. laser-based distance measurement devices);

3) Ultrasonic motion sensors (e.g. reflection delay devices); and

4) RF motion sensors (e.g. interferometers).

[0022] Any of these sensor types may be used to produce a signal that is processed by signal processor 70 to eliminate noise and the like through techniques such as quadrature detection, filtering and signal averaging. The resulting signal is fed to the "valid motion stimulation" detector 80 including, for example, a correlator or an adaptive filter that is also given the timing of the stimulation pulse from TMS stimulator 20 to determine whether the detected movement is a valid TMS induced motion or the result of incidental patient initiated movement. Detection of the valid stimulus may then be reported directly to the operator (visual signal, audible signal, or displayed message) as in the prior art embodiments of Figures 1 and 2 (see dashed line 85). Alternatively, as shown in Figure 3, the signal may be provided to a processor 50 that operates a search algorithm such as PEST to determine the next stimulation level to try and to indicate convergence. The output of this algorithm may then be provided to the operator 10 who sets the new value for the next iteration.

[0023] Figure 4 illustrates a further embodiment in which the operator 10 is removed from the feedback loop. In this embodiment, the TMS stimulator 20 of Figure 3 is provided with sufficient intelligence and processing power that it may incorporate the valid motor stimulation detector 80 and the search algorithm processor 50. The enhanced TMS stimulator is identified as element 20' in Figure 4. As shown, the enhanced TMS stimulator 20' may also include TMS power electronics 90 for providing the stimulation signal to the stimulation magnet 30 as well as a stimulator central controller 100 that is responsive to the search algorithm 50 to generate control signals that seek convergence to find the motor threshold value. Another variation on the motion sensor method proposed here is the use of more than one sensor 60 at more than one

location so that motion can be narrowed to a particular muscle group that moved in response to a stimulation signal. This is important since stimulation of certain portions of the motor cortex results in movement of large muscle groups, such as the arm or whole hand. Proper determination of the TMS motor threshold requires isolation of specific muscles so that the setting of the level is repeatable from session to session.

Evoked Potential and EMG Detection Methods

[0024] Other proposed aspects of the invention include replacing motion detection sensors 60 of Figures 3 and 4 with direct motor evoked potential (MEP) measurement devices that measure an induced neurological voltage and correlate the measured neurological voltage to the TMS stimulus. This can be done by using an EMG system to detect a waveform and using a signal processing algorithm or simple threshold detector to determine a valid stimulus. This technique has been widely used by many researchers, but it requires a sophisticated user and equipment to avoid problems with signal interpretation. Use of this method to detect a valid signal and using it in a closed loop control scheme has been proposed by the developers of PEST. However, specific details to make such an implementation practical have not been communicated in known prior art. The present inventor has recognized that a successful implementation requires allowing for capacitor charging and/or discharging times after the target stimulation has been set by the controller. A delay is required or, alternately, early responses can be ignored. Because of the high degree of artifact in EMG signals requiring significant operator interaction to set up the equipment correctly and to successfully detect a valid stimulus from a highly varied and complex waveform, MEP and EMG are not used in preferred embodiments of the invention.

[0025] The MEP embodiment of the invention further recognizes a variation on the EMG approach that includes setting the TMS stimulation level without using the motor cortex. Instead, the TMS coil associated with the stimulation magnet 30 is positioned and the stimulation level is adjusted both by indirectly measuring the evoked potential or the corresponding change to the EEG waveforms when the dorsolateral prefrontal cortex (DLPFC) is stimulated. The latter form would be the ideal approach for TMS since it avoids the motor cortex motor threshold procedure entirely. Studies that correlate EEG waveforms to DLPFC stimulation levels have not been thoroughly done at this time. However, the literature recognizes changes in EEG waveforms and quantitative EEG measures corresponding to neurological conditions, such as major depression.

Non-Motion Detection Methods

[0026] Another embodiment of the invention includes the detection of a signal other than one caused by physical motion (i.e. thumb twitching) which also has a reasonable and strong correlation to stimulation of the motor cortex. The following possible signals are proposed:

a) Left/right asymmetry changes in a narrow subset of EEG leads placed preferably on the forehead of the patient; and

b) Fast autonomic responses that are directly detectable (e.g. skin conductivity, modulation of respiration, reflex responses).

[0027] In such an embodiment, the sensors 60 of Figures 3 and 4 would be replaced by EEG detection devices and/or by fast autonomic response detectors that measure skin conductivity, modulation of respiration, reflex responses, and the like. These are signals typically used in a polygraph. Skin conductivity is measured with a pair of electrodes in contact with the skin and connected to a calibrated ohmmeter. Respiration can be measured with an expandable bellows placed around the subject's chest. The bellows is attached to a pressure sensor or (rarely) a flowmeter to detect a respiration signal. This signal is electronically processed to determine periodicity which is the respiration rate. The rate can be calculated as a rolling average which may be time correlated with a cortical stimulation. Reflex responses could be measured with motion sensors similar to those described above.

Non-Motor Cortex Methods

[0028] There are potentially other radically different methods of determining the appropriate stimulation level for TMS studies other than the motor cortex motor threshold methods. These methods rely on the determination of two parameters: cortical depth and neuronal excitability. Several means for determining depth are described here. One such means is using a localized ultrasound probe (or separate angled transmit and receive transducers) to determine depth of cortical tissue at the treatment site. This measurement then may be correlated to the motor cortex methods discussed above to test accuracy and repeatability of the method. For example, motor threshold may be determined for a particular patient using the visual detection of thumb twitch. The cortical depth can then be performed at the same site using an ultrasound (or other) technique. A neuronal excitability index, NE, can be calculated as: NE = MT/Depth. The depth can now be determined at the treatment site and the MT value calculated as MT = NE*Depth. This may be more accurate than assuming the MT is the same for MT and therapy sites, as is done in most studies at this time. Alternatively, a NE may be developed using other means such as EMG, or cognitive assessment tools. Once this technique has been

calibrated against a standard MT method, depth can be measured and multiplied by the NE to get MT.

[0029] Another alternative technology to measure cortical depth is the use of a localized impedance probe or a coil and detection circuit whose Q factor changes with tissue loading. This technique operates on the principle that coil loading (or alternatively RF power absorption) varies with cortical depth. This approach may require transmission of low power RF signals and determining attenuation levels or reflections from the cortical surface, or just simply doing a very accurate measurement of coil loading. In addition, this approach may be applied at multiple sites to determine a baseline or variations from the motor cortex area to the TMS therapy area. For example, depth may again be combined with a NE as described above to determine MT.

[0030] Alternatively, a localized and specifically designed probe may be used to detect impedance changes or filling factor differences when the probe is placed on the scalp at the desired treatment site. Such a probe may be constructed using a tuned coil and detection circuit that is sensitive to loading differences encountered when different biological tissue is placed in its proximity. The probe may be calibrated by observing impedance or Q factor (i.e. frequency*inductance/resistance) at a location where cortical depth is known from other methods such as ultrasound or standard motor threshold methods. Linearity and sensitivity must be determined by conducting these observations over a range of tissue depths, locations and subjects. An alternative variation of this probe is to transmit a radiofrequency (RF) pulse through this tuned circuit to the patient's head at the proposed stimulation site and observe the absorbed power compared to that at a known cortical depth. These methods rely on loading differences between cerebral spinal fluid and cortical tissue and therefore require a high degree of sensitivity and appropriate calibration. Once the cortical depth is determined the neuronal excitability may be estimated by a number of standard neurological and/or psychological measures, including but not limited to EEG signal analysis (or subset thereof), measurement of autonomic response times, and depth of awareness measures (e.g. Aspect Medical, Inc. bispectral index or BIS™).

[0031] It is to be understood that the foregoing illustrative embodiments have been provided merely for the purpose of explanation and are in no way to be construed as limiting of the invention. Words used herein are words of description and illustration, rather than words of limitation. In addition, the advantages and objectives described herein may not be realized by each and every embodiment practicing the present invention. Further, although the invention has been described herein with reference to particular structure, materials and/or embodiments, the invention is not intended to be limited to the particulars disclosed herein. Rather, the invention

extends to all functionally equivalent structures, methods and uses, such as are within the scope of the appended claims. Those skilled in the art, having the benefit of the teachings of this specification, may affect numerous modifications thereto and changes may be made without departing from the scope and spirit of the invention.